Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
345767D20796		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/FR2004/000086	16.01.2004	17.01.2003
International Patent Classification (IPC) or national classification and IPC		
A61K 31/57, A61P 25/00		
Applicant		
MAPREG		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

   ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

   ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

   _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11-10-2004	06-12-2004
Name and mailing address of the IPEA/	Authorized officer
Facsimile No.	Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FR2004/000086

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-19 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. _____ as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* 1-12 received by this Authority on 04.10.2004 with the letter dated 27.09.2004

nos.* _____ received by this Authority on _____

☒ the drawings:

sheets 1/7-7/7 as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	6-7, 11-12	YES
	Claims	1-5, 8-10	NO
Inventive step (IS)	Claims	6-7	YES
	Claims	1-5, 8-12	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents:

D1: US-B-6 245 757 1;

D2: WO 01/68068 A;

D3: WO 02/36128 A;

D4: MURAKAMI K ET AL, PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, 2000, vol. 97, no. 7, pages 3579-3584, XP002257452.

Unless otherwise specified, reference is also made to the relevant passages of these documents as cited in the international search report.

V.2.1

(a) D1 describes the use of neurosteroids and, in particular, pregnenolone methyl ether in the treatment of cell lesions caused by ischaemia. The composition can be administered orally or parenterally using a carrier that facilitates the rapid transfer of the steroid to the brain. The concentration of active principle can vary from 5

to 1,000 mg. Since pregnenolone is a molecule that comprises only one hydroxy group in position 3, the present Authority considers that pregnenolone methyl ether and 3-methoxy-pregnenolone are identical molecules. It follows that claims 1-5 and 8-10 are not novel over D1 (PCT Article 33(2)).

(b) D2 describes the use of pregnenolone (PREG), Δ5-pregnene-3β, 20α-diol, 3β-hydroxy-5α-pregnane-20-one, PREG tosylate, 5α-pregnane-3β, 20α-diol, PREG-acetate, PREG-16α-methyl, PREG-16β-methyl, Pregna-16α-17α-methylene and Pregna-5-ene-3β, 20β-diol-16α, 17α-methylene in the treatment of Alzheimer's disease, vascular dementia, the consequences of vascular trauma and accidents on the nervous system, neurodegenerative diseases and nerve cell ageing. The compositions as per D2 contain 100 to 500 mg of active substance and can be administered orally or injected. The compounds are capable of passing through the blood-brain barrier, of binding to the same site as pregnenolone on the proteins constituting or associated with the cytoskeleton elements, and of displacing the pregnenolone bound to MAP2, whereby they can influence microtubule assembly and stabilisation.

D3 describes the use of PREG hemisuccinate and PREG carboxy methyl ether in the treatment of neurological diseases, for example, memory-related

diseases such as Alzheimer's, amnesia, substance-induced memory loss, epilepsy, Parkinson's disease, ischaemia, and spinal chord lesions and pain. The substances as per D3 can be administered orally or parenterally at doses of between 10 and 1,000 mg and can pass through the blood-brain barrier.

Like D2, D4 describes the novel mechanism of action of neurosteroids and, in particular, PREG, Δ5-pregnene-3β, 20α-diol and 3β-hydroxy-5α-pregnane-20-one, during *in vitro* binding experiments on rat brain cytosol. These steroids bind to the neuronal protein associated with MAP2 microtubules, and increase the speed and extent of the resulting *in vitro* tubulin polymerisation with purified proteins, which form microtubules that appear to be normal under an electronic microscope.

(c) It follows that D2-D4 do not anticipate the novelty of claims 1-12 of the present application because they do not relate to pregnenolone derivatives carrying a 3-methoxy function.

(d) The present Authority would also like to add the following observation with regard to document D1:

According to the present application, the 3-methoxy-pregnenolone is no longer capable of converting itself into metabolites with a

progestational activity (cf. page 3, lines 17-25). However, D1 relates to the use of "progestins" to treat damage caused by ischaemia and cites 3-methoxy-pregnenolone as one of these progestins (column 5, lines 4-5). It could, therefore, be concluded that there is no support for the 3-methoxy-pregnenolone cited in D1. However, there are no indications in D1 that could justify the assertions that 3-methoxy-pregnenolone no longer has any progestational activity, that it is therefore not a "progestin" and that D1 is not part of the prior art.

(e) In conclusion, only claims 6-7 and 11-12 appear to be novel over the prior art documents (PCT Article 33(2)).

V.2.2

Claims 11-12 do not, however, involve an inventive step because the use of PREG derivatives is already known in the treatment of neurological and/or neurodegenerative diseases, as are the mechanisms of action thereof. As a result, a person skilled in the art aware of D1-D4 could easily infer that, like other PREG derivatives, 3-methoxy-PREG increases stabilisation, induces microtubule polymerisation and increases neurite growth in a cell (PCT Article 33(3)).

Claims 6 and 7 involve an inventive step because the use of 3-methoxy-PREG, substituted with a

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

dichloromethyl or 3β-methoxy-5α-pregnane-20-one in 17α, in the treatment of neurodegenerative diseases is not described or suggested in D1-D4 (PCT Article 33(3)).

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/FR2004/000086

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
EP 1 310 258	14.05.2003	08.11.2001	

See Supplemental Box.

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

Box No. VIII **Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The following feature in claim 8 has been omitted from the description: "or of a derivative molecule" (cf. page 10, lines 1-3 and PCT Article 6).

Claim 7 should be dependent on claims "1 to 4", not "1 to 5".

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Box VI:

D5 (EP 1 310 258) describes the use of 3β-methoxy-pregn-5-ene-20-one, 3β-methoxy-5α-pregnane-20-one as well as PREG, pregn-5-ene-3β, 20α-diol, and 3β-hydroxy-5α-pregnane-20-one in order to enhance cognitive functions and memory in patients suffering from memory loss induced by age, a lesion, or a neurological, neuropsychiatric or neurodegenerative disease (Alzheimer's disease, dementia, etc.). The compositions as per D5 can be administered orally or parenterally.